## REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 1-9 and 11-16 are pending; claims 1-9, 11-14, and 16 are currently under examination, and claim 15 is withdrawn. Without acquiescence or prejudice, claims 1-3, 6, 8, 13, and 16 are amended to particularly point out and distinctly claim certain embodiments of Applicants' invention and to correct certain typographical errors, and claim 7 is canceled. No new matter has been added by the amendments. Support for the amendments can be found in the specification as originally filed, for example, at page 10, lines 6-15, which describe a "variable region" of an immunoglobulin (Ig); page 13, lines 10-11; page 24, line 26; page 38, lines 6-7; page 45, line 19; and Table I at page 43, the latter of which describes various constructs that lack a "portion" of a hinge region.

With respect to the exclusion of a "variable region" in claim 1, it is respectfully noted that if an element is positively recited in the specification, then it may be explicitly excluded in the claims. *See* M.P.E.P. § 2173.05(i), citing *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.").

It should also be noted that these amendments are made without prejudice to prosecution of any subject matter described in the instant application in a related divisional, continuation, continuation-in-part, or re-issue application.

### REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

Claims 2-8 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The Examiner agrees that the specification enables methods of producing immunoglobulin (Ig) constant regions such as IgG, IgA, IgM, IgE, and IgD; ii) IgG1, IgG2, IgG3, and IgG4, as well as CH1, CH2, CH3, and CH4 or CL, but asserts that it does not enable the production of "combinations and hybrids thereof."

Applicants traverse this rejection and submit that persons skilled in the art could practice the full scope of the instant claims without undue experimentation, *i.e.,* using nothing

more than routine experimentation. Applicants also respectfully disagree with each of the Examiner's bases for maintaining this rejection, as set forth in the instant Action.

Nonetheless, without acquiescence, the instant claims have been amended to delete the recitation "combinations and hybrids thereof," which Applicants believe to obviate this rejection. Applicants therefore submit that the instant claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of this rejection.

**REJECTIONS UNDER 35 U.S.C. §103**

A. Claims 1 and 11 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Capon *et al.* (U.S. Application No. 2003/0104535) in view of Reilly *et al.* (U.S. Application No. 2005/0048572). The Examiner asserts that both Capon *et al.* and Reilly *et al.* teach methods of transforming prokaryotic cells to express an immunoglobulin (Ig) constant region having an *E. coli* derived signal peptide, and culturing the cells to express the Ig constant region for purification. The Examiner further asserts that Reilly *et al.* teach additional signal sequences, including the STII sequence of SEQ ID NO:36. The Examiner then asserts that it would have been obvious to follow the teachings Capon *et al.* to include the *E. coli* derived signal peptide sequences of Reilly *et al.*, and would have had a reasonable expectation of success in practicing the presently claimed subject matter.

B. Claims 1 and 11 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Capon *et al.* in view of Reilly *et al.*, in further view of Kwon *et al.* (U.S. Patent No. 6,605,697). The Examiner asserts that Kwon *et al.* teach the STII peptides of SEQ ID NOS: 36-46, and then asserts that it would have been obvious to follow the teachings of Capon *et al.* and Reilly *et al.* to include the *E. coli* derived signal peptide sequences of Kwon *et al.*

Applicants traverse each of the rejections in sections A and B above and submit that the instant claims satisfy the requirements of non-obviousness. Mainly, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

At a minimum, it must be demonstrated that the combined references teach or suggest all the claim features, and even assuming, *arguendo,* that the combination of references teach each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). Here, as previously made of record, the cited references fail to teach or suggest methods of producing an Ig constant region, by transforming *E. coli* with a recombinant expression vector including a nucleotide sequence encoding a signal sequence isolated from *E. coli* and a nucleotide sequence encoding ***an Ig constant region, without a variable region***, culturing a resulting transformant, and isolating and purifying the Ig constant region expressed by the transformant, wherein the signal sequence is a heat-stable enterotoxin II signal sequence, and wherein ***the Ig constant region is expressed in the cytoplasm in a water soluble form***.

The cited references in combination fail to teach or suggest all the claim features. For one, these references fail to teach or suggest an *E. coli*-based expression system having a nucleotide sequence that encodes a heat-stable enterotoxin II signal sequence fused to ***an Ig constant region without a variable region***. Instead, Capon *et al.* mainly disclose the use of the herpes gD glycoprotein in mammalian expression systems, such as to express CD4. Reilly *et al.* do not remedy the defects of Capon *et al.*, as this reference, at best, describes a prokaryotic expression system for ***complete or whole antibodies*** (*see* abstract of Reilly *et al.*; and Simmons *et al.*, *Journal of Immunological Methods*. 263:133-147, 2002, the corresponding research article to Reilly *et al.*, enclosed herewith), as opposed to the Ig constant regions, without a variable region, of the present invention. Kwon *et al.* is similarly deficient, as this reference merely suggests the expression of human growth hormone (hGH), among a few other proteins, none of which include an Ig constant region. Applicants recognize that the cited references cannot be attacked individually, but nonetheless submit that these references, in combination, must still teach or suggest all the claim features. Since none of these references even remotely refer to an Ig constant region without a variable region, whether in combination with a heat-stable

enterotoxin II signal sequence or otherwise, these references fail to provide the minimum elements of a *prima facie* case of obviousness.

Further, the cited references in combination fail to teach or suggest a method of producing an Ig constant region, without a variable region, in which the Ig constant region is ***expressed in the cytoplasm in a water-soluble form***. In this regard, Applicants respectfully disagree with the Examiner's assertion that such a property is inherent in the methods of the cited references (*see* the Action, page 14). First, it is kindly submitted that to rely on an inherency theory, the burden of proof lies with the Examiner to provide extrinsic evidence that ***makes clear*** that the missing descriptive matter (*i.e.,* an Fc fragment that is expressed in the cytoplasm in a water-soluble form) is ***necessarily present*** in the method of Capon *et al.*, Reilly *et al.*, or Kwon *et al.* *See* M.P.E.P. § 2112 (IV), citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Inherency may not be established by ***probabilities*** or ***possibilities***, and the mere fact that a certain characteristic ***may*** occur or be present in the prior art is ***not sufficient*** to establish the inherency of that characteristic. *Id.* Here, other than referring to the alleged use of SEQ ID NO:36 in Reilly *et al.*, the Examiner has provided no technical reasoning to ***make clear*** that an Fc fragment, without a variable region, would be ***expressed in the cytoplasm in a water-soluble form*** when fused to a heat-stable enterotoxin II signal sequence.

On this last point, Applicants submit that the alleged use of SEQ ID NO:36 in Reilly *et al.* does not ***make clear*** that the results of the instant methods are ***necessarily present*** in the teachings of the cited references (*see* the Action, page 14). Rather, Applicants submit that certain protein expression characteristics, such as localization and post-translational processing, may depend on more than just the regulatory elements relating to protein expression (*i.e.,* SEQ ID NO:36), as relied upon by the Examiner. Indeed, as is the case here, these characteristics may depend, at least in part, on the specific protein being expressed, such as an Ig constant region without a variable region, as presently claimed. The instant specification evidences that very result, by utilizing a ***structure*** that differs from any of the constructs in the cited references, *i.e.,* a signal sequence fused to an Ig constant region without a variable region, as compared to the full-length antibody of Reilly *et al.*, and by showing that this new ***structure*** is directed to a different more useful intracellular compartment – the cytoplasm. The cited references contain no

basis to predict this result, because they simply do not suggest such a ***structure***. Instead, Reilly *et al.* merely teach that their whole antibody-based expression vector is used for the "***periplasmic secretion*** of heavy and light chains" (*see, e.g.,* page 25, paragraph 216) (emphasis added). This limitation of Reilly *et al.* is emphasized by Simmons *et al.* (*supra*), which refers to the periplasmic secretion of ***full-length antibodies*** (*see* abstract). Similar to Reilly *et al.*, Kwon *et al.* merely describe additional signal sequences with enhanced secretion efficiency into the ***periplasmic space*** (*see, e.g.,* abstract and column 2, lines 34-38), and, thus, fail to remedy the deficiencies of Capon *et al.* and Reilly *et al.* In this light, Applicants submit that there is nothing inherent in the use of SEQ ID NO:36 with respect to achieving cytoplasmic expression of a polypeptide of interest, such as an Ig constant region without a variable region, as presently claimed.

Further, it is respectfully submitted that the cited references fail to provide any apparent reason to practice the presently claimed subject matter with a reasonable expectation of success. These references provide no technical basis whatsoever to envisage the cytoplasmic, water-soluble protein expression of an Ig constant region without a variable region, especially in view of the fact that Reilly *et al.* teach that antibody heavy or light chains fused to a signal sequence are secreted into the periplasmic space. Thus, even if persons of ordinary skill in the art combined the teachings of these references, such persons would not have arrived at the presently claimed methods, since none of these references teach or suggest fusions of Ig constant regions without a variable region, nor do they teach or suggest methods that have been shown to yield cytoplasmic, and not periplasmic, water-soluble protein expression of Ig constant regions. Rather, a whole new line of experimentation would have been required to practice the instant methods, with nothing to predict the successful practice thereof, as empirically demonstrated by Applicants. Since the cited references fail to teach or suggest each feature of the instant claims, and further fail to provide any reasonable expectation of practicing the presently claimed subject matter, then these references fail to establish a *prima facie* case of obviousness over the instant claims.

Further, as previously made of record, the non-obviousness of the instant claims is supported by relevant secondary considerations, including evidence of improved properties

and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996). For example, the instant methods offer improvements over conventional methods of secreting whole antibodies into the periplasmic space, such as by allowing enhanced expression efficiency, among other advantages (*see, e.g.,* page 26, line 25 to page 28, line 13 of the specification). Also, according to the claimed methods, the specification provides experimental evidence supporting the improved and unexpected cytoplasmic, water-soluble expression of Ig constant regions without variable regions (*see, e.g.*, Example 4; and Figure 1). Since none of these improved properties or unexpected results are found or suggested in the cited references, inherently or otherwise, nor are the ***structural features*** of the expression vectors and encoded polypeptides that lead to these unexpected results, Applicants submit that this evidence provides relevant secondary indicia of non-obviousness, thereby supporting the patentability of these claims.

Therefore, in view of the failure of the cited references to teach or suggest each feature of the instant claims, and/or to provide any reasonable expectation of arriving at the claimed methods, as well as the improved properties and unexpected results shown by Applicants for such methods, Applicants submit that instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103, and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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Enclosure:
Simmons *et al.*, *Journal of Immunological Methods*. 263:133-147, 2002.

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